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Chronic pain: experimental medicine and clinical insights

FORUM workshop, December 2021

Jointly hosted by the Academy of Medical Sciences, the British Neuroscience Association, The Physiological Society, and Versus Arthritis

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British Neuroscience Association

The Physiological Society

VERSUS ARTHRITIS

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All web references were accessed in November 2022.

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Executive summary

Chronic pain is estimated to affect up to 43% of the UK population. This is likely to rise with the increasing ageing population and prevalence of comorbidities, as well as with the ongoing COVID-19 pandemic. On the Friday 10 December 2021, the Academy of Medical Sciences, the British Neuroscience Association, The Physiological Society and Versus Arthritis convened experts across academia, clinicians, industry and patients to discuss chronic pain, its impacts on individuals and the emerging science for the understanding of and potential treatments for chronic pain.

A key focus of the meeting was how to put people with lived experience of chronic pain at the heart of chronic pain translational research. Participants highlighted a range of methods to do so, including the following:

- **'Reverse' or 'backwards' translation** – beginning with understanding chronic pain in humans and working backwards to inform studies. This pathway has the potential to re-invigorate the development of interventions and treatment for chronic pain.
- **Improved phenotyping[1] of pain** in people living with chronic pain is an essential step to better understand underlying mechanisms.
- However, **phenotyping is challenging** for several reasons, including the subjective nature of pain, a lack of objective measures of pain and a difficulty in linking these directly to underlying biological drivers, such as genetic variations.
- In addition to biological phenotyping, psychological factors are extremely important too; there is **a need to better understand some of the psychological comorbidities** that occur as a consequence of pain or that may increase vulnerability to chronic pain.
- **The factors involved in the initiation and exacerbation of chronic pain are complex**, including both psychological and physiological factors that contribute towards the onset and maintenance of chronic pain. There may be shared mechanisms of producing and maintaining pain, although participants noted that there are no clear answers at present, with evidence for distinct mechanisms provided by pre-clinical research.
- In practice, bringing together the biomedical and psychological fields can be challenging. At pain clinics, there can be a disconnect between services. **Multidisciplinary approaches to facilitate collaboration between these two fields of physiology and psychology** will be necessary to gain a holistic view of the mechanisms and causes of chronic pain.

Participants also discussed how clinical studies may need to change, and the role of researchers and regulators in supporting these changes:

- **Novel trial endpoints are needed**, which must be acceptable to both people living with chronic pain and regulatory bodies.[2] Generating appropriate endpoints, and deciding how to measure these endpoints, needs to be done in collaboration with people living with

[1] Phenotype refers to an individual's observable traits, such as height, eye colour and blood type. A person's phenotype is determined by both their genomic makeup (genotype) and environmental factors. https://www.genome.gov/genetics-glossary/Phenotype

[2] An endpoint is the primary outcome that is being measured by a clinical trial. https://friendsofcancerresearch.org/glossary-term/clinical-trial-endpoints

chronic pain and **requires the involvement of patient communities and others as part of a research team.**

- **Endpoints could also consider other measures of impact.** For example, activities that provide people with a sense of joy and meaning (such as dance therapy) tend to require more qualitative than quantitative measures but may be valuable examples of the efficacy of a therapy.

Participants discussed the role and challenges associated with the use of animal models in chronic pain research:[3]

- Animal models have been widely used to study pain; however, they have not always translated to effective treatments in humans.
- This is often due to the complex nature of human chronic pain and the limited mechanical threshold measures, such as reliance on evoked pain behaviour in animal research.
- There is an opportunity to utilise animal models more effectively to benefit translational chronic pain research, including exploring the use of a greater variety of animal pain assessments.
- Beneficial models include preclinical longitudinal studies, which utilise measures such as assessment of spontaneous/ongoing pain, cognitive deficits, anxiety-like and depressive-like behaviour.

Participants also reflected on recruitment and research methodologies for clinical studies:

- In clinical studies, **a combination of quantitative and qualitative methods is likely the best approach**, though there was the recognition that qualitative, subjective experiences can be harder to measure. Digital technologies, such as wearable devices or journalling on mobile phone apps, were suggested as options to capture different aspects of the experience of living with chronic pain. For example, wearable devices can help with the measurement of more nuanced aspects of pain experience, such as sleep disturbance.
- **Recruitment strategies need to be diverse in their approaches to avoid excessive self-selection of participants.** For example, people's lived experiences differ at different parts of their journey; this and other aspects of an individual's holistic experience should be considered to provide a broad spectrum of experience.

Participants highlighted a number of important factors to help provide more effective treatments in the future. These included a need to standardise and enhance the quality of data collection to enable effective use, as well as a need to improve understanding of the complex multifactorial mechanisms of chronic pain, including both the physiological and psychological mechanisms involved. Better consideration of the experience of people living with chronic pain is essential to fully understand how scientific phenotypes of chronic pain translate into disruption of people's lives.

The meeting also emphasised the need for greater collaboration between industry, regulatory agencies, academia, patients, and the healthcare system to improve the understanding of chronic pain and the development of new treatments. Participants suggested that a formal international network of neuroscientists, immunologists, sports scientists, psychologists, representatives from industry, academia, the healthcare system, carers and people living with chronic pain, among others would be useful in driving forward progress in this field.

[3] For the Academy's statement and position on the use of animals in research please visit: https://acmedsci.ac.uk/policy/uk-policy/animals-in-research

Introduction

Chronic pain – pain that carries on for at least three months or longer – is estimated to affect up to 43% of the UK population and this is likely to rise with our increasing ageing population and prevalence of comorbidities.[4] In addition, the ongoing COVID-19 pandemic is likely to increase the number of people living with chronic pain, either due to the effects of 'post-COVID-19 syndromes' – the long-term effects of COVID-19 infection – or due to the exacerbation of existing conditions due to health service disruption or the mental and physical stress of lockdown and physical distancing.

Despite the prevalence of chronic pain, treatment options are limited. Treatment options for neuropathic pain include amitriptyline, duloxetine, gabapentin, or pregabalin, which need to be titrated, and the response and tolerability carefully monitored.[5] Treatment options are often repurposed or 'off licence' drugs.[6] The National Institute for Health and Care Excellence (NICE) guidelines demonstrate that the evidence for the effectiveness of current pain therapies is low, and that the risks often outweigh the benefits.[7]

Although there is a need for new, more effective therapies for chronic pain, the pipeline for new pain therapies has stalled. There have been several high-profile clinical failures of potential treatments that looked promising from preclinical studies but failed to translate into benefits in people living with chronic pain. For instance, the sodium channel $Na_v1.7$ has strong genetic linkage to pain in humans, but treatments targeting the channel to date have not proved successful in clinical trials owing to a difficulty in targeting it selectively, and an incomplete understanding of the fundamental neurobiology in pain circuits.[8] The failure of 'forward' translation of basic pain research into therapies has led the predictability and efficacy of preclinical pain studies to be questioned.

There is a need to learn from failures within the pain field and consider where new research could be most impactful in better understanding pain. One area of interest is 'reverse' or 'backwards' translation – beginning with understanding pain in patients and working backwards from this to inform therapies and mechanistic studies.

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[4] Fayaz A, *et al*. (2016). *Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies*. BMJ Open **6(6)**, e010364.
[5] NICE (2021). *Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain.* NICE guideline [NG193]. Published 07 April 2021. https://www.nice.org.uk/guidance/ng193
[6] Basbaum AI & Bráz JM (2016). *Cell transplants to treat the "disease" of neuropathic pain and itch*. Pain **157 Suppl 1**, S42-S47.
[7] NICE (2021). *Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain*. NICE guideline [NG193]. Published 07 April 2021. https://www.nice.org.uk/guidance/ng193
[8] Kingwell K (2019). *Nav1.7 withholds its pain potential*. Nature Reviews Drug Discovery **18**, 321-323.

This workshop explored the current landscape of translational chronic pain research and considered how clinical research, through experimental medicine, clinical insights and the experience of people living with chronic pain, can help provide new evidence to inform preclinical drug discovery. The workshop was jointly hosted by the Academy of Medical Sciences, the Physiological Society, the British Neuroscience Association and Versus Arthritis. It was chaired by Professor Irene Tracey FMedSci (Head, Nuffield Department of Clinical Neuroscience, Vice-Chancellor elect University of Oxford) and Dr Iain Chessell (VP & Head, Neuroscience, BioPharma R&D, AstraZeneca), and convened attendees from industry, academia, the healthcare system and beyond, including allied health professionals and people living with chronic pain. A participant list can be found in Annex 1. Workshop discussions were continued informally at a virtual networking session after the workshop themed on 'understanding chronic pain'; the networking session was attended by both workshop attendees and others with an interest in the chronic pain field.

The agenda for the workshop can be found in Annex 2. The objectives of the workshop were to explore how holistic insights from clinical research can:

- Inform new drug discovery programmes and new therapeutic interventions.
- Overcome the challenges of translating chronic pain research from *in vitro* to *in vivo* models.[9]
- Consider how cross-sector[10] collaboration, knowledge exchange and coordination between sectors can support development of treatments in chronic pain.

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences, nor its Fellows.

[9] For the Academy's statement and position on the use of animals in research please visit: https://acmedsci.ac.uk/policy/uk-policy/animals-in-research

[10] For the purposes of this report, 'sectors' refers to organisations and groups who have an interest in chronic pain, which spans (but is not limited to) academia, healthcare, industry, charities, patients, and the public.

The translational challenge

While developing a medicine is never simple, the chronic pain field is especially challenging owing to several factors, including a lack of understanding of underlying biology, few tractable biological targets, and difficulty in assessing and classifying the pain experienced by patients.

In his introductory presentation, **Dr Iain Chessell** (VP & Head, Neuroscience, BioPharma R&D, AstraZeneca) discussed several promising molecules with novel mechanisms to relieve pain – 'analgesic' mechanisms - that have been successful in animal models but have not translated into human clinical success. Indeed, industry-wide, the failure rate for small-molecule pain drugs has historically been approximately 90% by the Phase II clinical trial stage.

The most common reasons for these failures are a lack of objective evidence that the molecule engages its target in humans and the related challenge of finding a safe and tolerable dosage that is also effective. This has been a long-standing problem for the field – it is often difficult to know whether a small molecule is interacting with its target in humans. Even if the molecule is engaging its target, the margin between toxic effects and analgesic effects may be very narrow owing to the vital role that many pain-relevant biological targets have in the body, and their location in the central and peripheral nervous systems. Regulators may then set a lower limit for a safe dose, and so the molecule cannot be delivered at the concentration required to provide pain relief in patients.

While many of these targets have been discovered in an *in vitro* or animal model, the problem is not with the models themselves, but a lack of tools to truly understand the underlying biology of the targets in humans. Instead, a different approach is required, starting with a deeper understanding of chronic pain in patients, along with genomic and mechanistic studies.

Living with chronic pain

Throughout the workshop, the importance of understanding the life experiences and diverse needs of people living with chronic pain, and of bringing the insights of people living with chronic pain to research and clinical trials, was highlighted by presenters and participants.

Colin Wilkinson, one of the public contributors speaking at the workshop, described living with chronic pain for more than 20 years (Box 1). He proposed researchers and clinicians must consider the biological, psychological, and social impact of the causes of pain when developing treatments, as well as the consequences. Only by recognising the whole experience can researchers fully understand the processes that turn a signal travelling up a nerve into the disruption or dismantling of a person's life.

Clinicians, researchers, and people living with chronic pain all bring different insights to a collaboration. In recognition of the value of this expertise, Colin and others at the workshop proposed that all parties, including people living with chronic pain, need to contribute to decisions for collaborations to be effective.

Box 1: Chronic pain has affected every area of my life

'I started suffering from chronic pain 30 years ago, aged 18. I had pain in all my joints, as I do now.

In 2018, I had an X-ray-guided injection of steroid into my right hip. Previously, these had helped. After that, I was diagnosed with septic arthritis, an infection in the joint capsule, and was in extreme, unbearable pain and unable to move my leg. I had an operation leaving an 8-inch hole in my leg that began the worst six months of my life. It took three operations and six months of antibiotics to clear that infection, by which time I needed a hip replacement. I am still dealing with the physical and psychological consequences of that incident, partly because it emerged that the infection was caused by clinical negligence.

Living with the pain I have now is difficult. My underlying arthritis had already robbed me of many of the things I really enjoyed. I have now been robbed of what was left of my career, in pain that has profound effects on every area of my life. During the year between the injection and the hip replacement, I lost hope of regaining function, lost the ability to adapt to my condition, and couldn't see a positive way out of this. With counselling I am learning to adapt again in different ways, and to live with what happened to me.'

Pain really does affect everything – sleep, mood, sex, work, family, friends. Unless research captures and investigates pain holistically, we'll stay where we are now, with few effective treatments and a partial understanding of what's going on in people's lives.

Frances Borrer, a volunteer research partner from Versus Arthritis, described how she has lived with arthritic pain for more than 40 years (Box 2). The research challenge she highlighted was that of harnessing individual experiences to better understand why one drug or therapy works for one person and not for another. By doing so, people living with chronic pain could be offered personalised treatment plans, involving less trial and error – a more targeted approach.

Both Colin and Frances discussed the importance of the meaningful involvement of people living with chronic pain in research. Involving people actively and meaningfully from the outset, before anything is decided, is vital. Sustaining and enriching the relationship between researchers and people living with chronic pain throughout the research process is the key to success. To determine the research questions which need to be answered, questions such as these are useful:

- 'What matters most to you?'
- 'What's the one thing you want to change?'
- 'What would make the most difference?'

By talking to people living with chronic pain, both from a primary and secondary care perspective, researchers can forge relationships they can rely on throughout the lifecycle of their research, and the patients can become researchers' most important resource.

Box 2: The difference research can make

'I've been living with rheumatoid arthritis for 43 years and, lately, with osteoarthritis.

It is estimated that 43% of people in the UK suffer chronic pain because of a range of conditions. Each individual will tell of crying in frustration, trying and failing to open a tin, of not being able to do the poppers up on their son's baby-grow, of screaming in pain and waking in the night, or of the impossibility of putting on a pair of tights with fingers that have been swollen and painful for many years.

Every day it can feel like a battle, physically and mentally. On a good day, I hardly notice the pain, but on a bad day it is all I notice. And the exhaustion of trying to get through the day saps what energy I have.

How do I manage this chronic pain? Mostly through gritted teeth. In my experience, drugs for pain relief that do not 'space you out' don't take away the pain. And many medications have side effects that require further medication to manage them.

For me, anti-TNF was transformative. And while it too has its side effects and its challenges, it has changed my life and given me back the life I really wanted. So you'll understand why I'm passionate about the difference that research can make.'

New insights from cohorts, big data and genomics

Chronic pain represents a diverse range of conditions and experiences, where the underlying biological mechanisms may be complex and multifactorial. Professor David Bennett FMedSci (Professor of Neurology and Neurobiology, University of Oxford) discussed how several different techniques, including large-scale studies, can be used to understand these factors.

Professor Bennett's expertise is in neuropathic pain – pain that arises due to damage to the sensory nervous system. When trying to understand such pain by looking at groups of people living with the condition, the challenge is to balance the study of small groups of people in detail, versus studying very large cohorts. At the population level, very specialised tests are not possible, so large-scale studies often use questionnaire-based outcomes.

To understand the complexity of pain requires an array of different approaches. Approaches to explore the physical and physiological dimensions of pain include: measuring action potentials in peripheral nerves can give clues to the origins of maladaptive electrical signals; functional brain imaging can be used to look at brain activity; sensory profiling can look in more detail at different aspects of sensory symptoms; while quantitative sensory testing – which measures changes in sensitivity to different types of sensations (e.g. temperature, touch or pressure) – can provide a profile of the pattern of dysfunction within the sensory nervous system. A growing area is understanding some of the molecular changes in people's genetics that may predispose them to pain.

Exploring the relationship between psychological state and chronic pain is extremely important too; there is a need to build understanding of some of the psychological comorbidities that occur as a consequence of, or increase vulnerability to, chronic pain.

Studies of non-freezing cold injury are an example of how researchers can go from understanding the features of a condition in humans to developing insight into the pathophysiology, and potentially also stratifying people who are most responsive to particular treatments (Box 3).

Box 3: Reverse translation in non-freezing cold injury ('trench foot')

Non-freezing cold injury – 'trench foot' – was described in the First World War. Soldiers exposed to cold and wet environments could develop an acute, severe pain in their feet. For some, this would become a lifelong problem, with re-exposure to cold often resulting in a recurrence of the pain. This problem still occurs today, particularly in Armed Forces personnel, and notably in people of Afro-Caribbean descent.[11]

Working with the Ministry of Defence, Professor Bennett and colleagues studied a cohort of soldiers suffering from non-freezing cold injury.[12] The patients scored highly in a screening tool for neuropathic pain (called DN4); they were hypersensitive to cold, and sensation was lost in the hands and the feet. Skin biopsies showed that nerve fibres in the skin were reduced. This led to the conclusion that non-freezing cold injury is a neuropathic pain condition, a sensory neuropathy triggered by an inciting event or exposure to cold and wet environmental conditions.

Understanding the pathogenesis of non-freezing cold injury led to the development of a grading system that can be used across the world. It also led to the Army implementing preventive procedures supported by validated diagnostic tests, allowing sufferers can get access to appropriate therapy for neuropathic pain. This has led to a reduction in cases.

Non-freezing cold injury has also been studied by a national consortium called BRIDGE, which uses whole-genome sequencing to examine people living with extreme pain disorders.[13] BRIDGE combined harmonised detailed phenotyping of people living with neuropathic pain across the UK with state-of-the-art genomics.

In the study, the most common group of genetic variants found to be clinically significant in contributing to pain were variants in voltage-gated sodium channels (Nav1.7, Nav1.8 and Nav1.9).[14] People with non-freezing cold injury had a much higher frequency of a particular variant in sodium channel (Nav1.7).

When the Nav1.7 channel was produced *in vitro*, at room temperature there was no electrophysiological difference between the wild-type and the variant. At colder temperatures, however, the variant channel showed increased excitability. This demonstrates a gene–environment interaction; people with this variant are more vulnerable to extreme temperatures, and so at greater risk of this condition when exposed to a cold, wet environment.

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[11] Vale TA et al. (2017). *Chronic non-freezing cold injury results in neuropathic pain due to a sensory neuropathy*. Brain **140(10)**, 2557-2569.
[12] Ibid, 2557-2569.
[13] https://www.ucl.ac.uk/centre-for-neuromuscular-diseases/research/experimental-clinical-trials/muscle/muscle-open-trials/bridge-neuropathic-pain-nihr-pain
[14] Themistocleous A.C et al. (2022) *Investigating genotype-phenotype relationship of extreme neuropathic pain disorders in a national cohort: 'NIHR Bioresources Rare Disease – Neuropathic Pain Disorders'.* Brain Communications. ISSN 2632-1297 (In Press). https://openaccess.sgul.ac.uk/id/eprint/114973/

To date, most successes in genomic studies of pain have been predominantly in rare genetic changes that have a large effect on function. However, neuropathic pain is common – it affects almost 10% of the general population – so is likely to be polygenic, with multiple genes interacting with the environment and with each individual gene having only a small effect.

The DOLORisk consortium aimed to understand neuropathic pain through genetics, psychosocial and clinical factors.[15] The consortium aligned how people were studied across Europe, which enabled issues to be studied at significant scale. Using genome-wide association studies, the DOLORisk consortium has identified a single nucleotide polymorphism, mapped to the gene SLC25A3, which appears to be modulating the risk of neuropathic pain.

These studies are now being extended in the PAINSTORM *(*Partnership for Assessment and Investigation of Neuropathic Pain: Studies Tracking Outcomes, Risks and Mechanisms) consortium as part of the Advanced Pain Discovery Platform.[16] Furthermore, the results of new pain questionnaires, compiled by UK-Biobank (having been completed by over 150,000 participants), will enable understanding of neuropathic pain at an even larger scale in a prospective cohort, not only from the perspective of genetics, but from investigating a multitude of demographic, clinical, and environmental factors.

Improvements in informatics, such as machine learning, can be used to examine multiple factors and their interactions. In a recent study of painful diabetic neuropathy,[17] some factors such as glycaemic control and body mass index (BMI) were related to neuropathic pain. The importance of psychological comorbidities, anxiety, and depression in the development of neuropathic pain was also clear.

The challenge is to integrate the data with the aim of stratifying people experiencing pain. This will provide a better understanding of the pathogenesis of pain, hopefully on an individual level, which will lead to more accurate diagnostics and prognostics and, ultimately, better treatment choices.

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[15] Pascal M.M.V, et al. (2019). *DOLORisk: study protocol for a multi-centre observational study to understand the risk factors and determinants of neuropathic pain.* Wellcome Open Research **3:63**, 1-22.
[16] https://www.ndcn.ox.ac.uk/research/neural-injury-group/research-projects/painstorm
[17] Baskozos G, et al. (2022). *Classification of painful or painless diabetic peripheral neuropathy and identification of the most powerful predictors using machine learning models in large cross-sectional cohorts.* BMC Medical Informatics and Decision Making **22:144**, 1-23.

Enhancing the use of animal models to support translation

Although animal models have been widely used in the study of pain, many targets fail the translational step from *in vitro* to *in vivo*, or from animal to human. Dr Sandrine Géranton (Associate Professor in Molecular Neuroscience in the department of Cell & Developmental Biology at University College London) is researching epigenetic mechanisms and environmental influences in the development of chronic pain conditions, as well as the role of stress regulators in the maintenance of long-term pain states. She discussed her work on enhancing the use of animal models to support translation.

When using animals to study pain, mechanical hypersensitivity – whether an animal has developed extreme sensitivity to touch – is often the main outcome measure used. However, in humans, chronic pain conditions (including chronic joint pain) affect people in different ways and are often accompanied by affective disorders – patients often discuss low mood, anxiety, tiredness, fatigue, lack of energy, and sometimes also memory impairment. Research studies in animals tend to focus on short time periods when considering the development of chronic pain, whereas chronic pain develops and affects humans over longer time periods.

In her research, Dr Géranton uses two different models of joint pain: one that induces ankle inflammation (the complete Freund's adjuvant (CFA)-induced inflammatory pain model) and one that induces knee inflammation (the monoiodoacetate (MIA) model). Both models are commonly used in chronic pain and joint pain research and induce a similar degree of functional deficit, though the knee pain model induces a larger weight-bearing deficit. These deficits are maintained in the long-term; Dr Géranton's studies run from three to six months, unlike many preclinical longitudinal studies that run from a few days to a few weeks.

Animals with knee pain tend to pay attention to the inflamed areas more than animals with ankle pain and show long-term cognitive deficits. Unlike animals with full cognitive function or those with ankle pain, animals will not pay increased attention to a novel object that has replaced a known object. Animals with knee pain also displayed more anxiety-like behaviour (affecting how much they explore an open area), depressive-like behaviour (affecting their preference for sucrose water), as well as a loss of motivation (or increased fatigue). These behaviour changes were studied for up to six months. These studies suggest that animal models of similar sensory deficits or functional deficits can present different types of emotional behaviour.

Characterising the animal models more fully – on a cognitive and behavioural as well as a physiological and genetic level – will help researchers assess the validity of pain-relieving therapies. For example, Dr Géranton's research about the interaction of stress and chronic pain uncovered a target for the treatment of chronic pain called FKBP51, a stress regulator.

Inhibiting this target reduced the mechanical sensitivity of animals with knee pain. Furthermore, after one month's treatment with an inhibitor, the depressive-like behaviour of the animals also improved. Even if the inhibitor was removed, and the hypersensitivity returned, the development of depressive-like behaviour was delayed.

For the Academy's statement and position on the use of animals in research please visit: *https://acmedsci.ac.uk/policy/uk-policy/animals-in-research*.

Informing new treatments for chronic pain

Participants discussed the importance of looking at both the physiological and psychological mechanisms involved in chronic pain for the development of new treatments.

Animal models have played an important role in the 'traditional' or 'forward' translation of basic pain research into therapies. Limitations in their use were discussed by participants, with questions raised about the use of evoked pain – how an animal responds to mechanical stimulus – as a general method of measuring pain in animals. They recommended that a greater variety of animal pain assessments be used, while recognising that it is not yet clear which assessments will be the most useful in the long term, and that such assessments can be time-consuming.

One such assessment involves animal movement. If humans are in pain, they tend to be less active. Similar behaviour is seen in animal models – they move in different ways when in pain – and researchers can use high-speed videography to capture animal movement in multiple dimensions.

Participants also discussed 'reverse' or 'backwards' translation – beginning with understanding pain in humans and working backwards from this to inform therapies and mechanistic studies. In humans, there is unlikely to be one single mechanism generating pain – the patient populations are extremely heterogeneous. Without better phenotyping, treatments are more likely to fail in clinical trials. The IMI-PAINCARE Consortium was raised as an example; their approach is to first phenotype people living with chronic pain, then develop subpopulations, and then do backwards translation to the animal models.[18]

However, there are challenges to these approaches. Participants discussed the need for detailed phenotyping of pain in large cohorts of people, and how best to discern mechanisms from large datasets of disease insights from humans. Also noted were issues with genetics-led approaches to target identification, due to the subjective nature of pain and how outcomes are reported. Improved objective measures of pain were seen as particularly important.

Understanding the full experience of people living with chronic pain, including both the physiological and psychological mechanisms involved in chronic pain, was highlighted as important in the development of new treatments. Both psychological and physiological factors contribute to the onset and maintenance of chronic pain, particularly of disability and stress, although participants noted that there are no clear answers at present.

Participants discussed how expectations of pain can affect chronic pain, how pain-related worry and fear can drive avoidance behaviours, and how these are linked to pain-related disability and the stress that comes with pain. The long-term effects of pain-related stress were raised, and the support of people with pain by creating better, more inclusive environments rather than modulating the stress response, particularly in situations where there is discrimination.

[18] https://www.imi-paincare.eu/

The challenges of bringing together medical and psychological approaches to tackling pain were discussed. At pain clinics, there can be a disconnect between the physiological and psychological aspects of care, with doctors providing medicine and psychologists focusing on day-to-day dealing with pain. There can also be resistance to certain modalities of treatment – for example, to psychological treatments options.

Studies of psychological mechanisms are being incorporated in some research trials, with depression and anxiety measured using questionnaires. However, participants noted that questionnaires have limitations as they reduce the experience of people living with chronic pain to a set of questions that may not be applicable to everyone. The PAINSTORM project has discussed such challenges with lived experience partners, including how questionnaires can lack personal relevance.[19]

[19] https://www.ndcn.ox.ac.uk/research/neural-injury-group/research-projects/painstorm

Ensuring that clinical trials in chronic pain generate appropriate evidence

Clinical trials are designed to determine whether interventions or treatments are safe and effective in people. As chronic pain is particularly individually unique and subjective, participants discussed the challenges in generating robust, repeatable evidence and in recruitment for such trials.

Participants recognised that the starting point for clinical trials needs to be talking and listening to people living with chronic pain, hearing about their lived experience of chronic pain. These lived experiences can differ markedly depending on the cause. For example, the lived experience of visceral pain from irritable bowel syndrome differs from that of musculoskeletal joint pain.

Hence, a key issue discussed was how to ensure that endpoints are acceptable to people living with chronic pain as well as being useful to regulators. Choosing appropriate endpoints, and deciding how to measure these endpoints, needs to be done in collaboration with people living with chronic pain. This requires the involvement of patient communities and others as part of a research team.

As there can be a lot of variation in patient populations, participants discussed the need to focus more on deep phenotyping and outcome measures. While participants felt that the best approach would be to use a combination of quantitative and qualitative methods, there was the recognition that qualitative, subjective experiences can be harder to measure. Digital technologies, such as wearable devices or digital journalling on mobile phone apps, were raised as options to capture different aspects of a person's experience of living with chronic pain. For example, wearable devices can help with measurement of more nuanced aspects of pain experience, such as sleep disturbance.

Questions were raised about how different kinds of evidence are valued. Activities that provide people with a sense of joy and meaning – through dance therapy, for example – tend to require more qualitative than quantitative measures.

While qualitative studies tend to involve smaller numbers of patients, with fewer issues around recruitment, challenges with recruiting large numbers of people for clinical trials were raised during discussion. There was also the recognition that people who are involved in clinical trials can be a self-selected group, potentially introducing bias or leaving certain groups of patients unrepresented. Participants stressed that recruitment strategies therefore need to be diverse in their approaches, considering the different personal reasons to participate in a trial and what support different people living with pain might need to enable trial participation. The evolution of people's lived experiences over time also needs to be taken into account to get a broad spectrum of lived experience.

The Scottish Health Research Register (SHARE) was raised as an example of best practice. This is a register of people aged 11 and over who are willing to be invited to take part in research projects and have also consented to allow SHARE to use any remaining blood for the purposes of health research and healthcare improvement following routine clinical testing.[20] It was also noted that, in the field of cancer research, it is the norm for people to be included in clinical trials as part of their treatment (along with the potential benefits this comes with). Such inclusion is much rarer for conditions like chronic pain, despite many people living with chronic pain being engaged and interested in being involved.

In addition to engaging and involving people living with chronic pain in research, participants also discussed issues related to the quality of the evidence, namely ensuring rigour and validity in preclinical and clinical data. Participants highlighted the importance of being able to systematically assess many sources of evidence, and of providing consistency across questionnaires. Without this, it is difficult to combine datasets, reducing the pool of evidence to draw from.

[20] https://www.nhsgresearchanddevelopment.scot.nhs.uk/share/

Stimulating knowledge exchange, collaboration, and strategic coordination

Collaboration between industry, regulatory agencies, academia, people living with chronic pain, and the healthcare system would allow for more effective forward and reverse translation. However, a range of issues with coordination and engagement in the field were raised by participants.

Participants discussed the importance of collaborating with people living with chronic pain and other dedicated groups so that research approaches are aligned with the symptoms considered most important by people living with chronic pain.

Versus Arthritis and the Crohn's and Colitis Foundation were both noted as having good networks for collaboration. The need to involve populations that do not normally engage with research was raised – for example, people who do not speak English as a first language.

Some researchers noted that preclinical research can be perceived as less relevant to the public, because the application of the findings to patients is less obvious. Therefore, in these cases, more effort to engage with people living with chronic pain is required, including articulating the importance of understanding the underlying causes of conditions to the rational design and discovery of treatments. Others described having research partners who live with chronic pain and have a science background, helping bring both academic understanding and lived experience to the collaboration.

Many people living with chronic pain have comorbidities, so a broad range of expertise across healthcare systems is required in collaborations. There is also a need to improve data harmonisation in the healthcare system, so that data can be shared appropriately while ensuring patient confidentiality.

Participants discussed the importance of increased opportunities for engagement with regulatory agencies. As noted above, such agencies set the criteria that determine much of the focus for the research field.

For researchers, the GSK Immunology Network was noted as a successful network of immunologists around the world. An equivalent for the chronic pain field was proposed – a formal network of neuroscientists, systems neuroscientists, molecular neuroscientists, immunologists, cognitive neuroscientists, sports scientists, psychologists, representatives from industry, academia, the healthcare system, and people living with chronic pain. Existing organisations cited included the International Association for the Study of Pain and the Global Alliance of Partners for Pain Advocacy (GAPPA) Task Force.[21,22]

[21] www.iasp-pain.org
[22] www.iasp-pain.org/group/global-alliance-of-partners-for-pain-advocacy-gappa-task-force

Conclusion

Traditional preclinical models of researching chronic pain have not always resulted in effective applications in humans. Participants at the meeting highlighted that preclinical animal models could be improved by exploring a greater variety of pain assessments and using animal models that capture the long-term and psychological effects of different kinds of chronic pain. However, the causes, mechanisms and consequences of chronic pain in humans are complex and multifactorial, involving interaction between the physiology, psychology and environment of a person living with chronic pain.

There is a need to better understand the holistic experience of people living with chronic pain, including both the physiological and psychological mechanisms of chronic pain. This understanding can inform preclinical pain research, including the improvement of preclinical models of chronic pain, and help researchers understand how scientific phenotypes translate into the disruption or dismantling of a person's life as a consequence of living with chronic pain. Such understanding can help to inform treatments for chronic pain, including both drugs and other kinds of treatments that aim to alter and improve the environment of the patient.

To ensure meaningful evidence capturing the holistic experience of people living with chronic pain is gathered, participants emphasised the importance of involving people living with chronic pain in the design of studies and clinical trials and to capture qualitative as well as quantitative data about the experience of chronic pain. A balance needs to be struck between standardising data collection to allow comparison between or combination of datasets, and ensuring the data collected reflects the spectrum of experiences of chronic pain.

The important work of many consortia in the pain field was described through the presentations and discussion. The overarching message from this workshop was the necessity to build on this to enable greater collaboration of healthcare practitioners and researchers from academia and industry with people living with chronic pain to enhance the research and development of treatments for chronic pain.

Annex 1: Attendee list

- **Dr Stephen Alexander**, Associate Professor of Molecular Pharmacology, University of Nottingham
- **Anoushka Anand**, Patient Representative
- **Dr David Andersson**, Reader in Physiology and Lecturer, King's College London
- **Dr Sibtain Anwar**, Consultant and Associate Professor of Cardiac Anaesthesia, Intensive Care and Pain Medicine, St. Bartholomew's Hospital and Barts Heart Centre
- **Tim Atkinson**, Public contributor
- **Dr Kirsty Bannister**, Senior Lecturer and Principal Investigator, King's College London
- **Professor David Bennett FMedSci**, Professor of Neurology and Neurobiology, University of Oxford
- **Merethe Blandhol**, Research Assistant, University of Oxford
- **Anthony Blockeel**, Research Fellow, University of Bristol
- **Professor Fiona Boissonade**, Professor of Oral Neuroscience, University of Sheffield
- **Frances Borrer**, Public contributor
- **Robin Brittain**, Patient Representative
- **Lisa Broad**, Senior Director, Eli Lilly and Company
- **Dr Liam Browne**, Sir Henry Dale Fellow, University College London
- **Dr David Bulmer**, Lecturer, University of Cambridge
- **Carolann Cassidy-Skinner**, Public contributor
- **Dr Iain Chessell**, VP & Head, Neuroscience, BioPharma R&D, AstraZeneca (**co-chair**)
- **Professor Lesley Colvin**, Clinical Professor (Teaching and Research) of Pain Medicine, University of Dundee
- **Professor Dame Jessica Corner FMedSci**, Pro-Vice-Chancellor for Research and Knowledge Exchange, University of Nottingham
- **Dr Silvana De Pirro**, Postdoctoral Researcher, Linköping University
- **Dr Diarmuid Denneny**, Lead Physiotherapist, University College London Hospital & Chair, Physiotherapy Pain Association
- **Professor Lucy Donaldson**, Professor of Sensory Physiology, University of Nottingham
- **Dr Robert Drake**, Senior Research Associate, University of Bristol
- **Dr Jim Dunham**, NIHR Clinical Lecturer in Anaesthesia, University of Bristol
- **Professor Justin Durham**, Head, School of Dental Sciences, Professor of Orofacial Pain & Honorary Consultant Oral Surgeon, Newcastle University
- **Dr Noam Epstein**, Neuroscience Discovery Medicine Physician, GSK
- **Dr Sandrine Geranton**, Associate Professor of Cell & Developmental Biology, University College London
- **Professor Thomas Graven-Nielsen**, Director, Center for Neuroplasticity and Pain (CNAP), Aalborg University, Denmark
- **Dr James Hockley**, Investigator, GSK
- **Dr Shirley Hopper**, Medical Assessor, Medicines and Healthcare products Regulatory Agency (MHRA)
- **Professor Emily Jefferson**, Director, Health Informatics Centre, University of Dundee
- **Dr Martin Johnson**, Clinical Lead for Chronic Pain, Royal College of General Practitioners, & Vice President (Membership), British Pain Society
- **Catrina Kivlin**, Public contributor
- **Laura Klinkhamer**, PhD student, University of Edinburgh
- **Dr Jenny Laird**, Vice President of Search & Evaluation, Eli Lilly and Company

- **Dr Jo Latimer**, Head of Neurosciences and Mental Health Board, Medical Research Council
- **Dr Charlotte Lawrenson**, Senior Research Associate, University of Bristol
- **Stephen Lee**, Patient Representative
- **Dr Ian Lewis**, Head of Strategy and Initiatives, National Cancer Research Institute
- **Dr Lisa Lione**, Associate Professor of Translational Pharmacology, University of Hertfordshire
- **Professor Bridget Lumb**, Professor of Systems Neuroscience, University of Bristol
- **Dr Emma Meehan**, Assistant Professor, Coventry University
- **Samantha Morris**, Psychotherapist, Integrated Psychotherapies
- **Paulina Nunez-Badinez**, Postdoctoral Researcher, Bayer AG
- **Dr Anthony Pickering**, Wellcome Trust Reader in Neuroscience, University of Bristol
- **Christine Price**, Patient Representative, Physiotherapy Pain Association
- **Dr Krishma Ramgoolam**, Postdoctoral Researcher, University College London
- **Professor Andrew Rice**, Professor of Pain Research, Imperial College
- **Professor Cormac Ryan**, Professor of Clinical Rehabilitation, SHLS Allied Health Professions, Centre for Rehabilitation, Teesside University
- **Professor Philippa Saunders FRSE FMedSci**, Professor of Reproductive Steroids, The University of Edinburgh
- **Dr Annina Schmid**, Associate Professor, University of Oxford
- **Dr Whitney Scott**, Senior Lecturer in Clinical Health Psychology, King's College London
- **Dr Sadhana Sharma**, Head of Strategy, UKRI-BBSRC
- **Dr Emanuele Sher**, Research Fellow, Eli Lilly and Company
- **Dr Mike Short**
- **Professor Blair Smith**, Professor of Population Health Science, University of Dundee
- **Professor Ewan Smith**, Professor in Nociception, University of Cambridge
- **Dr Jina Swartz FMedSci**, Therapeutic Area Head Neuroscience and Executive Medical Director, Merck Sharpe & Dohme (MSD)
- **Professor Irene Tracey FMedSci**, Head, Nuffield Department of Clinical Neuroscience, University of Oxford (**co-chair**)
- **Georgia Turner**, PhD student, University of Cambridge
- **Christin Veasley**, Founder and Director, Chronic Pain Research Alliance
- **Dr Katy Vincent**, Senior Pain Fellow, University of Oxford
- **Professor David Walsh**, Professor of Rheumatology & Co-Director, Pain Centre Versus Arthritis, University of Nottingham
- **Dr Fraser Welsh**, Senior Director, AstraZeneca
- **Colin Wilkinson**, Public contributor
- **Professor David Wynick**, Professor of Molecular Medicine and Honorary Consultant Physician, University of Bristol

One other public contributor also participated in the workshop. However, they preferred to remain anonymous.

<u>Staff and secretariat</u>

- **Eren Akademir**, Policy Intern, Academy of Medical Sciences
- **Dr Yasmin Allen**, FORUM Policy Manager, Academy of Medical Sciences
- **Rachel Bonnington**, Engagement Officer, Academy of Medical Sciences
- **Melissa Bovis**, Engagement Manager, Academy of Medical Sciences
- **Mr Craig Bullock**, Senior Transformational Research and Partnership Lead, Versus Arthritis
- **Mr Joseph Clift**, Head of Policy and Campaigns, British Neuroscience Association

- **Clare Farmer**, Research Programme Manager, Versus Arthritis
- **Dr Alice Fletcher-Etherington**, Policy Officer, Academy of Medical Sciences
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- **Andrew Mackenzie**, Head of Policy and Communications, The Physiological Society
- **Dr Giles Newton**, Deadlift Media Ltd
- **Holly Rogers**, Head of Engagement, Academy of Medical Sciences
- **Dr James Squires**, Head of Policy (Interim), Academy of Medical Sciences
- **Angel Yiangou**, Policy Manager, Academy of Medical Sciences

Annex 2: Agenda

Reinvigorating the development of interventions of chronic pain through back translation	
13.00	**Introduction from co-chairs** Professor Irene Tracey FMedSci, Professor of Anaesthetic Neuroscience, Warden Merton College & Pro-Vice Chancellor, University of Oxford & Dr Iain Chessell, VP & Head, Neuroscience, BioPharma R&D, AstraZeneca
	Session 1: Clinical insights and innovations to invigorate the field
13.10	**The translational challenges of medicines development in chronic pain** Dr Iain Chessell, VP & Head, Neuroscience, BioPharma R&D, AstraZeneca
13.25	**The patient experience** *Short talks from two public contributors, highlighting their experiences managing chronic pain and the need for new and better interventions.* • Colin Wilkinson • Frances Borrer
13.40	**Cohorts, big data and genomics providing new insights** Professor David Bennett FMedSci, Professor of Neurology and Neurobiology, University of Oxford
13.55	**Enhancing the use of animal models to support translation** Dr Sandrine Geranton, Associate Professor of Cell & Developmental Biology, University College London
14.10	**Q&A with the speakers** Chaired by Professor Irene Tracey FMedSci
14.25	**Short break**
	Session 2: Integrating back translation into intervention development
14.30	**Breakout session: Disseminating, adopting and embedding new evidence sources into the development of interventions for chronic pain** *A break-out session involving all attendees to allow smaller group discourse to answer questions about how we can expand and embed reverse translation approaches into the sector.* 1. What mechanisms do we have confidence in from preclinical and clinical research to help inform new treatments for chronic pain? What needs to be done to further validate their utility? Are there new approaches we should be taking to better identify new mechanisms and targets? 2. How do we stimulate the knowledge exchange, collaboration, and strategic coordination required between industry, regulatory agencies, academia and the NHS to allow for effective forward and reverse translation? 3. How do we ensure that clinical trials in chronic pain generate appropriate (subjective and objective) evidence, meet the needs of patients and are able to recruit effectively within the UK context?
15.30	**Short break**
15.40	**Reporting back and plenary session**
16.50	**Summary and chairs' remarks**
17.00	**Workshop close** Workshop participants move over to the Remo platform.
17.00	**Session 3: Networking session** Hosted on the virtual networking platform, Remo.
17.15	**Workshop summary and chair's remarks** *For the benefit of those at the networking event who did not participate in the workshop.*
17.30	**Unstructured virtual networking using the Remo platform**
18.30	**Close**

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